REMARKS:

Claims 1, 4-7, and 9-15 are pending in this application and stand rejected. Claims 23-621 are newly added in substitution of the rejected claims. The support for these claims are detailed in the table at the end of these Remarks. Applicant respectfully submits that no new matter has been added by way of this amendment.

Applicant thanks the Examiner for the interview of April 9, 2001. As requested during the interview, Applicant has obtained English translations of Japanese Patent Applications Nos. 05255088 and 05194225, which are included in a Supplemental Information Disclosure Statement that will be hand delivered to the Examiner in the next several days. Applicant is also providing the Examiner with a complete set of references cited in previous information disclosure statements, which the Examiner informed Applicant were misplaced by the PTO.

As established below, Applicant submits that the new claims are patentable over the prior art.

Rejections Under 35 U.S.C. §102(b)

The Examiner rejected now cancelled claims 7,10 and 12 as being anticipated by Lovgren et al. U.S. Patent No. 4,786,505 or by Ooishi et al. Japanese Patent Application No. 05255088. However, Applicant's new Claims 23 – 621 to pharmaceutical dosage forms and compositions are not anticipated by these references, nor by Ooishi et al. Japanese Patent Application No. 05194225. These references are directed to formulating intermediate cores, which are converted to enteric coated dosage forms—not to dosage forms that release the PPI in the stomach as claimed by Applicant. The dosage forms and compositions of Claims 23-237; 292-429 and 461-590 of the present invention are free of enteric coatings and therefore are not shielded from interacting with gastric acid secretions, and are specifically designed for disintegration and

dissolution in the stomach whereas the enteric forms disintegrate and dissolve in the duodenum. The dosage forms of Claims 238-291; 430-460 and 591-621 employ enteric-coated PPI (and optionally non-enteric-coated PPI) with a non-enteric-coated buffering agent in an amount of about 4 mEq to about 30 mEq. These forms have the dual action of release of buffer (and non-enteric-coated PPI if it is also used) in the stomach for an antacid effect, and release of enteric-coated PPI in the duodenum. The advantages of the inventive forms over the enteric-coated forms of the prior art are stated at pages 32-41 and 66 of the specification and include more rapid drug absorption, and an antacid effect by the buffering agent.

Importantly, none of the cited references teach the oral administration of the uncoated intermediate cores, nor do the cores meet the limitations of the Claims. The intermediate cores, therefore, are not "dosage forms" as claimed because a "dosage form" is defined as a completed form of a pharmaceutical preparation. Dorland's Medical Dictionary, 26th Ed. p. 218 (1988). Consequently, there is no teaching that such intermediate cores interact with gastric secretions to form the composition as claimed by Applicant. Indeed, the prior art teaches that such cores must have enteric coatings.

More specifically, the Lovgren '505 Patent teaches enteric coated forms having central cores with alkaline reacting substances to create a "micro-pH" around each omeprazole particle to protect the acid labile omeprazole from the acidic enteric coating polymers used to make the finished dosage forms. Lovgren '505 Patent, columns 3-5. Lovgren emphasizes that due to the instability of omeprazole in acidic and neutral media, "an oral dosage form of omeprazole must be protected from contact with the acid reacting gastric juices in order to reach the small intestine without degradation." Col. 1, ln. 35-39. The protection referred to by Lovgren is enteric coatings—not the buffering systems of the present invention. Indeed, Lovgren states: "In order

to obtain a pharmaceutical dosage form of omeprazole which prevents omeprazole from contact with acidic gastric juice, the cores **must** be enteric coated." Col. 1, ln. 48-51 (emphasis added). Further teaching away from the present invention, Lovgren states:

> If a conventional formulation of omeprazole is made, the stability is not satisfactory, particularly in resistance to humidity, and special moisture-proof packing has been adopted to minimize the troubles. However, this provides no satisfactory solution to the problems in today's drug distribution system, and also leads to increased costs. Under the circumstances, there has been a demand for the development of new enteric preparations of omeprazole with better stability.

Col. 2, ln. 14-23.

The "final dosage form" of Lovgren is "either an enteric coated tablet or capsule or in the case of enteric coated pellets, pellets dispensed in hard gelatin capsules or sachets or pellets formulated into tablets." Col. 5, ln. 60-64. Thus, the Lovgren '505 Patent does not teach dosage forms free of enteric coatings that interact with gastric acid secretions.

At the April 9th interview, the intermediate cores of the Lovgren '505 Patent were discussed in the context of Applicant's then pending claims to a pharmaceutical composition of a PPI and a buffer. As such, the Examiner requested Applicant to detail the amounts of the buffering agents taught by Lovgren. Applicant has done so below, and submits that Lovgren does not anticipate Applicant's new claims because they are directed to dosage forms employing significantly more buffer than that disclosed by Lovgren, and to compositions also comprising gastric acid secretions, a flavoring agent, an anti-foaming agent and buffer combinations.

The amount of buffering agent employed is critical to the ultimate bioavailability of the proton pump inhibitor (PPI). Without the benefit of the protection of an enteric coating, the buffering agent must be present in an amount sufficient to prevent or inhibit acid degradation of the PPI by gastric acid so as to achieve its bioavailability after oral administration. In the human

fasting stomach, one would expect to encounter about 5 mEq to about 20 mEq of acid depending on age or disease. Harrison's Principles of Internal Medicine, Ch. 238, pp. 1229-48 (12th Ed. 1991). Thus, depending on age and disease, about 5 mEq to about 20 mEq of the buffering agent is needed in a non-enteric-coated dosage form to neutralize such gastric acid before substantial degradation of the PPI occurs.

As shown in the table below, the Lovgren '505 Patent fails to teach any amount of buffer even close to 5 mEq.

Amounts of Buffers of Inner Cores of Lovgren '505 Patent (Col. 6, Table 1)

Example No.	mg Buffer	Mol. Wt.	Valence	Equiv.Wt.*	Total mEq +
1	none				0
2	15 mg disodium hydrogen phosphate (disodium phosphate)	142	2	71	0.21
3	15 mg magnesium oxide	40	2	20	0.75
4	15 mg magnesium hydroxide	58	2	29	0.52
5	15 mg magnesium hydroxide and 0.2 mg disodium hydrogen phosphate	58 142	2 2	29 71	0.52 + 0.002 = 0.522
6	15 mg magnesium hydroxide	58	2	29	0.52
7	15 mg synthetic hydrotalcite	602	18	35	0.43

* Equivalent weight is calculated as the molecular weight of the buffer divided by its valence.
+ Milliequivalents (mEq) are calculated by dividing the mg of buffer by its equivalent weight.

Consequently, the Lovgren '505 Patent does not anticipate Applicant's claims.

Likewise, the disclosures of Ooishi et al. Japanese Patent Application Nos. 05255088 and 05194225 do not anticipate the claims. Again, the emphasis of these references is on using buffering agents in an intermediate core part to prevent acid degradation of the PPI by the enteric coating. Specifically, Ooishi '088 teaches:

> An **enteric** preparation produced by coating a **core part** containing benzimidazole compound that has antiulcer action and is unstable in acid with **1-2 layers of undercoating**, and then applying an **enteric coating** agent thereupon, where the enteric preparation is characterized in that **aluminum hydroxide-sodium bicarbonate coprecipitate** or the aforementioned compound and **buffering agent** is blended **in the core part and/or undercoating layers**.

Abstract, p. 1 (emphasis added).

For the core part, Ooishi '088 teaches a stabilizer of aluminum hydroxide sodium bicarbonate coprecipitate in an amount of 0.1 to 20 parts to 1 part benzimidazole compound, and buffering agents in an amount of 0.01 to 2 parts to 1 part benzimidazole compound. Such buffering agents are defined as "sodium tartrate, sodium acetate, sodium bicarbonate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, trisodium phosphate or tripotassium phosphate." Ooishi '088, at [0010]. However, there is no teaching that such core parts are dosage forms suitable for oral administration without an enteric coating, nor that they react with gastric acid. Therefore, Applicant's claims are not anticipated by this reference.

Ooishi et al. Japanese Patent Application No. 05194225, which was filed within weeks after the '088 application, similarly focuses on preparing enteric coated dosage forms and intermediate core parts therefor. Specifically, the reference teaches a "preparation containing

stabilized antiulcer agent, formed by blending amino acid, amino acid acid salt or amino acid alkali salt used as stabilizer, along with buffering agent, with a benzimidazole compound that has antiulcer action and is not stable in acids." Ooishi '225, at claim 1. Ooishi '225 states that this preparation can be a "tablet, granule or capsule" Ooishi '225, at claim 5; [0004]. However, when read in context of the entire specification, such tablets, granules and capsules refer to intermediate forms that are then enteric coated for the finished dosage forms. This is emphasized by Ooishi '225's description of the prior art and problems to be solved by the invention:

> With preparations such as tablets, fine powders, granules, capsules and dispersions, the compounds are influenced by other components of the preparation formula and become unstable, leading to a decrease in content and discoloration over time. Among these preparations, **when the compounds are coated to produce granules, they have poor compounding properties with respect to enteric bases** (cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, polyvinyl acetate phthalate, and methacrylic acid acrylic acid copolymer), and suffer content decrease and discoloration. **When an oral preparation is to be manufactured** in this manner using benzimidazole compound, in addition to problems arising from the **need for compounding with other components and the use of enteric base coatings**, there are also difficulties with formulation due to the detrimental influences on stability as described above. Consequently, it is **necessary** to appropriately stabilize these compounds when they are to be formulated in oral dosage forms.

Ooishi '225, at [0001] (emphasis added).

Section [0004] on page 5 describes how the intermediate core compositions are obtained by uniformly blending the benzimidazole compound, the amino acid, amino acid acid salt or amino acid alkali salt stabilizer, the buffering agent, additives, and water. Amounts of these substances are in the ranges of 0.01-10 parts by weight of amino acid and 0.01-10 parts by weight of buffer with respect to 1 part by weight of benzimidazole compound. The reference states further that the "resulting mixture is then finely granulated with a wet granulator, and the

material is then subjected to tabletization to produce uncoated tablets for tablet production. Alternatively, the material can be granulated using an extrusion granulator, and then formed into core granules for producing granules." Ooishi '225, at [0004] (emphasis added). The application then states that "[t]he uncoated or core granules **obtained in this manner** can be formed into an enteric preparation by coating the core granules with enteric coating," and that:

> The **enteric tablet or granule** that is of a dosage form that is **appropriate for oral administration** can be obtained as described above, and in addition, the granules can be packaged into capsules to produce a capsule. The **preparation obtained in this manner** experiences little change in external appearance even over long-term storage, and exhibits excellent stability with almost no decrease in content. As a result, the preparations can be used in the treatment of digestive ulcers in mammals including humans.

Ooishi '225 at [0005].

There is thus no teaching in Ooishi '225 that the intermediate tablets and granules are suitable for oral administration. Indeed, it is only the enteric "preparation obtained in this manner" from the passage above at [0005] that is appropriate for oral administration and can be used to treat digestive ulcers. Therefore, it does not anticipate Applicant's claims.

Additionally, the Lovgren and Ooishi references contain no disclosure regarding the use of flavoring or anti-foaming agents in any of the claimed dosage forms. Moreover, because there is no teaching as to the oral administration of the intermediate cores, Applicant's method claims are likewise not anticipated. Similarly, Applicant's claims to two-part dosage forms (with or without enteric-coated PPI) are not anticipated by these references because there is no teaching to use buffering agents to surround the PPI in a non-enteric coated dosage form, or to use non-enteric-coated buffering agents in combination with enteric-coated PPI.

Rejections Under 35 U.S.C. § 103

The Examiner rejected now cancelled claims 1, 4-6 as being obvious over Pilbrandt et al., Andersson et al., Landahl et al., and McCullough CA 123:237886 (flavoring, simethicone). Claims 7-14 were rejected as being obvious over Lovgren '505, Ooishi '088 and Gergely CA 123:208914 (flavoring). Applicant's new claims, however, are not obvious in view of the cited art.

Lovgren '505, Ooishi '088 and Ooishi '225 do not render obvious Applicant's new claims to solid dosage forms and compositions, or the methods for using the same in the treatment of acid-related gastrointestinal conditions. As detailed above, these references teach away from Applicant's claimed invention by emphasizing that suitable dosage forms must employ buffering agents **and** enteric coatings. There is thus a teaching away from the interaction in the stomach of a PPI and the low pH gastric secretions. Such teaching away rebuts obviousness. See In re Sponnoble, 405 F.2d 578, 587 (CCPA 1969); In re Caldwell, 319 F.2d 254, 256 (CCPA 1963).

Until now, those skilled in the art thought that the administration of an acid labile PPI without an enteric coating to be unworkable. Applicant recognized the problems associated with the delayed release dosage forms (e.g., lack of liquid forms, difficulty in swallowing by children, elderly and critically ill, slow onset of action, difficulty of manufacture, etc.) and solved them by the present invention. Consequently, Applicant's claims to dosage forms, compositions and methods employing non-enteric-coated PPI are not obvious.

Because of such a lack of expectation of success for dosage forms released in the stomach, the use of flavoring agents and anti-foaming agents such as simethicone are also non-

obvious. According to the Federal Circuit in In re Oetiker, 977 F.2d 1443, 1447 (Fed. Cir. 1992, "[t]here must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination." Here, as shown above, the prior art tells the skilled artisan that PPIs must be enteric-coated and, therefore, there was no reason or suggestion to use flavoring agents or anti-foaming agents because such agents would serve no purpose with the enteric-coated forms of the prior art. Thus, Gergely and McCullough fail to render Applicant's claims obvious.

Applicant also submits that its claims to liquid pharmaceutical compositions are not obvious over Pilbrant, et al., Andersson, et al., Landahl, et al., Gergely and McCullough. Applicant's product by process claims are directed to combining the novel dosage forms and compositions with an aqueous medium. Pilbrant teaches a suspension of 60 mg omeprazole (micronized) in 50ml of water containing 8 mmoles of sodium bicarbonate. Andersson teaches omeprazole solutions created by dissolving the drug in a sodium bicarbonate/PEG400 solution. Landahl also teaches the dissolution of omeprazole in a solution of sodium bicarbonate and PEG 400. Consequently, none of these references teach or suggest combining a dry dosage form of PPI and a buffer with an aqueous diluent. Indeed, with the prior art teaching that non-enteric-coated forms are unstable to humidity (See Lovgren '505 patent, Col. 1-2), and that they must be enteric-coated, there was no expectation that such forms would be stable, let alone that they could be used to create liquid forms. Therefore, Applicant's claims are patentable over the cited art.

Support in Specification for New Claims

Per the Examiner's request, the support for the new generic claims are detailed in the table below.

Claim No.	Support Exists at Least on These Pages
23-94	24, 26-46
95-140	24-46
141-180	24-46
181-202	24; 34-36; 48
203-237	34-36
238-265	24; 27; 66
266-291	24; 27; 66

Claims 292-625 to omeprazole and lansoprazole correspond to the above generic claims, and support can be found for the same on these pages.

This application is now in condition for allowance. The Examiner is encouraged to contact the undersigned with any questions or to otherwise expedite prosecution.

Respectfully submitted,

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